Maraviroc (Celsentri) in HIV treatment

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BRIEF DRUG PROFILE

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INTRODUCTION

Since 1996, the prognosis of people living with immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) has improved significantly, due to highly active antiretroviral therapies (HAART) based on a combination of 3-4 anti-HIV drugs; the use of these drugs can achieve a durable suppression of HIV viraemia, turning HIV infection into a chronic illness. The three first licensed classes of antiretroviral agents are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Until recently, treatment options for individuals developing resistance to these drugs have been limited, but new drugs in existing classes (second generation NNRTIs and novel PIs) and novel classes of drugs (integrase inhibitors, CCR5 antagonists and fusion inhibitors) have become clinically available.

INDICATIONS AND DOSING

Maraviroc (MVR) is the first antiretroviral agent belonging to the new pharmacological class of CCR5-antagonists to be approved by the US Food and Drug Administration. MVR, in combination with other antiretroviral products, is indicated for adult patients infected with only CCR5-tropic HIV-1 virus strains resistant to multiple antiretroviral agents, and in presence of demonstrated active viral replication. This drug is available in film-coated tablets containing 150 or 300 mg of MVR; the recommended dose is of 150, 300 or 600 mg (depending on co-administered antiretroviral therapy and potential drug-drug interactions) twice daily. Tropism testing is required before initiation of treatment. MVR is currently included by AIFA (*Agenzia Italiana del Farmaco*) in a drug efficacy and safety monitoring program.

PHARMACOKINETICS

Pharmacokinetics of MVR is not influenced by gender, race or weight; age appears to influence MVR clearance, but the studied range (18-54 y) is very limited and insufficient data is available for the elderly. MVR can be taken with or without food, although a plentiful breakfast can considerably reduce its bioavailability. Dose adjustment is required in patients with renal impairment who are taking CYP3A4 inhibitors, and caution is needed in case of renal, hepatic or cardiac function problems.

Absorption			
Bioavailability	**Cmax**	**Tmax**	**Binding to plasma proteins**
23% at a 150 mg dose, 33% at a 300 mg dose	638 ng/ml	0.5 to 4 h (mean 2-3 h)	73-78% (albumin and alpha-1 acid glycoprotein)
Metabolism and distribution			
Volume of distribution	**Metabolism**	**Enzimes**	**Metabolites**
194 l	Hepatic	CYP3A4	Inactive
Elimination			
Clearance	**Plasma terminal half-life**	**Elimination**	**Interactions**
44 l/h	14-18 h	76.4% feces, 19.6% in urine (over 168 h)	CYP3A4 and/or P-glycoprotein inducers or inhibitors; St. John's wort.

Table I

Absorption, distribution, metabolism and elimination of maraviroc after oral administration

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Study	Design	Efficacy (at week 24)	Safety
MOTIVATE 1	Double-blind, randomized study comparing MVR + OBT qd vs MVR + OBT bid vs placebo + OBT (2:2:1) in 601 pts with CCR5-tropic HIV1	**HIV-RNA change from baseline (log_{10} cps/ml):** MVR qd: -1.88 MVR bid: -1.96 Placebo: -0.99 **VL < 400 cps/ml (%):** MVR qd: 55.1 MVR bid: 61.0 Placebo: 27.8 **VL < 50 cps/ml (%):** MVR qd: 44.0 MVR bid: 45.3 Placebo: 23.0	Treatment-related AEs occurring at a higher incidence than placebo (2% or 2-fold): abdominal pain, dyspepsia, muscle spams, myalgia, taste disturbance, cough and cutaneous rash.
MOTIVATE 2	Double-blind, randomized study comparing MVR + OBT qd vs MVR + OBT bid vs placebo + OBT (2:2:1) in 475 pts with CCR5-tropic HIV1		

Table II

Summary of main studies investigating efficacy and safety of maraviroc in HIV-1 patients. Dosage of maraviroc was 300 mg, or 150 mg for patient receiving protease inhibitors

AE = adverse events; CK = creatine kinase; cps = copies; MVR = maraviroc; OBT = optimized background therapy; pts = patients; VL = viral load

PHARMACODYNAMICS

HIV-1 strains can be categorized by their co-receptor tropism, i.e. their ability to use CCR5 (CCR5-tropic), CXCR4 (CXCR4-tropic), or both (dual-tropic) human chemokine receptors as co-receptors for entry into susceptible cells. MVR is a specific, slowly reversible, noncompetitive, small-molecule CCR5-antagonist, which acts by binding to the transmembrane region of this receptor, and stabilizing a conformation not recognized by the virus, which cannot enter host CD4+ cells. Resistance to MVR can occur by HIV mutagenesis, and was seen in both *in vivo* and *in vitro* samples.

EFFICACY AND SAFETY

MVR has demonstrated *in vitro* activity against a wide range of CCR5-tropic clinical isolates, including those resistant to the four currently existing classes of antiretroviral agents. Results of phase III clinical trials (MOTIVATE 1 and 2) demonstrate that this drug, in combination with optimized background therapy (OBT: 3-6 other antiretroviral products, excluding low-dose ritonavir), is superior to OBT alone in treatment-experienced patients infected with CCR5-tropic HIV-1, causing a significantly greater reduction in viral load and an increase in CD4+ cell count. In treatment-naïve patients, MVR formally failed to prove its non-inferiority to a standard regimen consisting of AZT/3TC + efavirenz after 48 weeks.

MVR appeared relatively well tolerated, with no particular concerns; in fact, no significant increases in cardiovascular events, hepatotoxicity, infections or malignancies have been reported. Several post-marketing, ongoing studies will assess the long-term safety on immune and liver function, malignancy, cardiac events, and risks associated with changes in tropism.

ECONOMIC EVALUATIONS

Currently, HIV treatment in Italy is based on HAART therapies, which consists in the mix of three or more antiretroviral agents. Possible combinations are made up of 2 NRTIs + 1 NNRTI, 2 NRTIs + 1/2 PIs, or 3 NRTIs. The daily cost of this therapy ranges from 15 to 28 €/die, with a mean of 22 €/die, for a monthly cost of about 650 €. This evaluation is based on dosages reported in the SPCs (Summary of Products Characteristics) and ex-factory prices.

As no alternative strategy can be identified, since MVR is to be added to standard OBT therapy, monthly pharmaceutical costs for this treatment are simply presented in Table III.

Tropism testing is required before the initiation of MVR treatment; Trofile™ HIV Entry Tropism Assay (Monogram), the test used in clinical trials, is delivered free of charge to hospitals by the drug manufacturer.

Packages	Cost/package (€)		Monthly cost (€)	
	Public	Ex-factory	<	>
150/300 mg, 60 cpr	1,340.55	812.25	812.25	3,249.00

Table III

Monthly pharmaceutical costs of maraviroc therapy in HIV treatment (Informatore Farmaceutico 2008)

Name of the Medicinal Product	Celsentri
Marketing Authorisation Holder	Pfizer
Active Substance	Maraviroc
Pharmaco-therapeutic Group	Other antivirals
ATC Code	J05AX09
Date of issue of Marketing Authorisation valid throughout the European Union	18 September 2007

REFERENCES

- Abel S, Jenkins TM, Whitlock LA, Ridgway CE, Muirhead GJ. Effects of CYP3A4 inducers with and without CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. *Br J Clin Pharmacol* 2008; 65: 38-46
- Abel S, Russell D, Taylor-Worth RJ, Ridgway CE, Muirhead GJ. Effects of CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. *Br J Clin Pharmacol* 2008; 65: 27-37
- AIFA – Agenzia Italiana del Farmaco – Elenco dei farmaci sottoposti a monitoraggio intensivo. Available on http://www.agenziafarmaco.it/allegati/farmaci_specialita_medicinale050808.pdf
- Carter NJ, Keating GM. Maraviroc. *Drugs* 2007; 67: 2277-88
- CELSENTRI – EPAR summary for the public
- CELSENTRI – Summary of product characteristics. Available on http://www.emea.europa.eu/humandocs/PDFs/EPAR/celsentri/H-811-PI-en.pdf
- CELSENTRI Scientific Discussion – European Medicines Agency (EMEA), 2008. Available on http://www.emea.europa.eu/humandocs/PDFs/EPAR/celsentri/H-811-en6.pdf
- Chan PL, Weatherley B, McFadyen L. A population pharmacokinetic meta-analysis of maraviroc in healthy volunteers and asymptomatic HIV-infected subjects. *Br J Clin Pharmacol.* 2008; 65: 76-85
- Dolin R. A new class of anti-HIV therapy and new challenges. *N Engl J Med* 2008; 359: 1509
- Emmelkamp JM, Rockstroh JK. Maraviroc, risks and benefits: a review of the clinical literature. *Expert Opin Drug Saf* 2008; 7: 559-69
- Fadel H, Temesgen Z. Maraviroc. *Drugs Today (Barc)* 2007; 43: 749-58
- Fätkenheuer G, Nelson M, Lazzarin A, Konourina I, Hoepelman A, Lampiris H et al. MOTIVATE 1 and MOTIVATE 2 Study Teams. Subgroup Analyses of Maraviroc in Previously Treated R5 HIV-1 Infection *N Engl J Med* 2008; 359: 1442
- Gazzetta Ufficiale della Repubblica Italiana – GU 271 – 5/4/2008. Supplemento ordinario – serie generale n.81
- Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; 359: 1429-41
- Hughes A, Barber T, Nelson M. New treatment options for HIV salvage patients: an overview of second generation PIs, NNRTIs, integrase inhibitors and CCR5 antagonists. *J Infect* 2008; 57: 1-10
- Informatore Farmaceutico 2008, Ed. Elsevier Masson, updated to June, 2008
- Maraviroc official FDA information, side effects and uses – Professional information. Available on http://www.drugs.com/ppa/entecavir.html
- Ministero della Salute. Commissione Nazionale per la lotta contro l'AIDS "Aggiornamento delle conoscenze sulla terapia dell'infezione da HIV". Indicazioni Principali per Soggetti Adolescenti o Adulti. Available on http://www.ministerosalute.it/imgs/C_17_pubblicazioni_718_allegato.pdf
- Ndegwa S. Maraviroc (Celsentri) for multidrug-resistant human immunodeficiency virus (HIV)-1. *Issues Emerg Health Technol* 2007; 110: 1-8

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2008: 128
- Zaniolo O. Efficacia e costi del trattamento con abacavir preceduto da screening per la reazione da ipersensibilità nell'infezione da HIV. *Farmeconomia e percorsi terapeutici* 2008; 9: 197-213

